CLINICAL ASPECTS OF CIGUATERA: AN OVERVIEW

TILMAN A. RUFF AND RICHARD J. LEWIS

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Ciguatera is a polymorphous disease posing important health, nutritional, economic and social problems for inhabitants of endemic areas, and occasionally for those in non-endemic areas. Limited progress has been made in understanding the pathophysiology of the disease and in developing effective treatment.

Clinical features of the disease are reviewed, and incidence, morbidity and mortality data are outlined. Methods to prevent ciguatera and progress in treatment of ciguatera are discussed, and key issues and needs for future research are described. These include: 1, consistent epidemiologic data, using a consistent case definition; 2, the human immune response to ciguatoxins; 3, the pathophysiological mechanisms underlying human disease, potentiation of disease by alcohol, and the phenomenon of sensitisation; 4, better tests for ciguatoxins; and 5, effective and safe treatment for affected patients.

Tilman A. Ruff, Department of Social & Preventive Medicine, Monash Medical School, Alfred Hospital, Commercial Road, Prahran 3181, Victoria; Richard J. Lewis, Southern Fisheries Centre, Department of Primary Industries, PO Box 76, Deception Bay, Queensland 4508; 22 November, 1993.

Ciguatera is the disease caused by the consumption of fishes contaminated with ciguatoxins, which originate from *Gambierdiscus toxicus* (Adachi & Fukuyo), a unicellular dinoflagellate alga associated with coral reefs (Adachi & Fukuyo,1979). Most toxic fish are captured during inshore fishing near coral reefs. Ciguatera is a circumtropical disease, likely to affect >25,000 persons annually. Its greatest impact is in Pacific island countries (Lewis,1992a). Although rarely fatal, possibly because fish succumb before concentrations lethal for humans can be accumulated (Lewis,1992b), its morbidity is considerable. Ciguatera has been reviewed several times (Gillespie et al.,1986; Lewis,1986; Hokama,1988; Vernoux,1988; Hokama,1991; Juranovic & Park,1991; Russell & Egan,1991; Lewis,1992a; Lewis & Ruff 1993).

Often regarded as an interesting tropical medical curiosity rather than a subject for serious medical study, a good deal of the clinical literature on ciguatera is rather repetitive and anecdotal and does relatively little to advance our understanding of the disease and its management.

Clinical manifestations of ciguatera are protean. In areas where the disease is not endemic, the diagnosis is often not considered by physicians unfamiliar with ciguatera, and a wide variety of erroneous diagnoses may be made, including neurosis. In many parts of the world, increasing international travel, and increasingly widespread transport and consumption of warm water fish, especially coral reef fish, make it more likely that cases will be seen outside endemic areas. The possible severity, chronicity and possibility of effective treatment make it important to consider the diagnosis in those presenting with a compatible illness soon after eating fish.

CLINICAL FEATURES

Clinical Manifestations

Ciguatera results in variable combinations of gastrointestinal, neurological, general and cardiovascular manifestations. Symptoms usually develop 1-6 hours after ingestion of toxic fish - in about 90% of cases within 12 hours (Gillespie et al,1986, Gillespie,1987), but in a few after more than 24 hours (Bagnis et al.,1979; Bagnis & Legrand,1983; Narayan,1980). Gut involvement usually consists of an acute self-limiting syndrome akin to gastroenteritis, which may be severe, but generally lasts less than 24-36 hours (Gillespie et al 1986, Gillespie,1987; Frenette et al.,1988; Engleberg et al.,1983). Symptoms may include abdominal pain, nausea, vomiting, diarrhea and tenesmus (rectal pain). Resulting intravascular volume depletion ('dehydration') and electrolyte disturbances may be severe, particularly in young children. Volume depletion and hypotension may be compounded by myocardial depression and disturbed vasomotor regulation (including deranged blood pressure control). Neuromuscular disturbances are most commonly sensory, but may also be motor. Although neurological dysfunction is typically sug-

gestive of predominant involvement of peripheral nerves, effects may occur at any level of the nervous system from cerebral cortex to muscle. Neurological manifestations are usually bilateral, but may be asymmetrical (Hamburger,1986) or unilateral (Hashmi et al.,1989). Manifestations may include coma, seizures, ataxia (disordered co-ordination and balance), cranial neuropathies including ophthalmoplegia (paralysis of eye movement), myelopathy (spinal cord dysfunction), peripheral sensory, motor and autonomic neuropathy and myositis (muscle inflammation).

Typical sensory symptoms are distal limb, perioral and lingual paraesthesia and dysesthesia (disordered sensation) - with prominent numbness and tingling - and often a very unpleasant form of hyperesthesia (abnormal, heightened sensation) particularly associated with cold objects producing a distressing burning sensation (Gillespie et al.,1986). Sometimes a reversal of temperature sensation occurs, such that cold objects feel hot and vice versa. Reduced distal sensation and reduced or absent tendon jerks are the commonest neurological signs. A sensation of fizzy, metallic taste may occur. Muscle weakness - most commonly distal or generalised, occasionally asymmetrical - sometimes involves bulbar and respiratory muscle groups. Airway protection and ventilatory support may be required in severe cases. Diffuse muscle pain is common, and may be associated with elevated blood levels of muscle enzymes and biopsy evidence of myositis (Nakano,1983).

General (non-localising) symptoms include malaise, lassitude, irritability, depressed mood, pruritus (itching), sleep disturbance and unusually vivid dreams. Headaches, arthralgia (joint pain, particularly involving shoulders, elbows, knees and ankles), pruritis (localised or generalised), dental pain, a sensation of looseness of the teeth and dysuria (painful urination) may also occur. A variety of skin rashes, most commonly maculopapular, are sometimes present and may be associated with desquamation (peeling) during the healing phase.

Bradydysrhythmias (slow cardiac rhythm disturbances), atrio-ventricular heart block, myocardial depression and loss of vasomotor regulation with hypotension, often postural, may occur during the early phase and tend to resolve more quickly than general and neurological symptoms. Autonomic dysfunction may be manifested by sweating, lacrimation (excessive tears), salivation and internal ophthalmoplegia (paralysis of ocular accommodation and pupillary responses).

Symptoms often fluctuate from day to day and at different times of day. The time course is generally one of improvement over days to weeks, but symptoms not uncommonly persist for months, or rarely years. Consumption of alcohol commonly exacerbates symptoms (Gillespie et al.,1986; Gillespie,1987). Death is rare (0.1% of recorded cases) (Gillespie et al.,1986; Juravnovic & Park,1991; Gillespie,1987; Bagnis et al.,1979; Bagnis & Legrand,1987). Clinical manifestations and severity may vary considerably, even among individuals poisoned by the same fish. In the absence of a specific human diagnostic test for ciguatera, this wide variation in clinical manifestations and the clinical nature of the diagnosis make reliability difficult. Diagnosis is especially difficult when only one person presents with less than a full hand of symptoms. Nerve conduction studies may be helpful, and demonstration of toxin in any remaining fish samples, while very useful, is often not possible. Commonly used clinical criteria for diagnosis of ciguatera are gastrointestinal and neurological symptoms following ingestion of potentially toxic fish. This combination, however, occurred in only 25/53 (55%) of patients in one common source outbreak (Engleberg,1983), and 52/57 (91%) of patients in another (Frenette,1988).

Person-to-person Transmission

Although the vast majority of ciguatera cases are caused by ingestion of toxic fish, various forms of person-to-person transmission have been described, and are indicative of the potent, persistent and lipid-soluble nature of ciguatoxins. These include: transmission via milk to breastfed infants (Bagnis & Legrand,1987; Thoman,1989; Blythe & De Sylva,1990), though hyperaesthesia of the nipples of a lactating mother may interfere with breast-feeding (Pearn et al.,1982); transplacental transmission, resulting in transient neurological manifestations in the newborn following maternal illness near term (Pearn et al.,1982); and apparent sexual transmission from female to male (penile pain after intercourse in the male partner of an affected woman) (Geller et al.,1991) and vice versa (pelvic and vaginal pain after intercourse in the female partners of affected men)(Lange et al.,1989).

Sensitisation and Recurrent Attacks

These are two of the most enigmatic aspects of ciguatera, and increase its morbidity as well as its social and economic consequences. Not only does immunity not follow an attack of ciguatera,

but there is evidence from a variety of locations that second and subsequent attacks tend to be more severe than first attacks (Bagnis et al., 1979). Also well documented is the phenomenon of sensitisation. Persons who have previously had ciguatera may suffer a recurrence of typical ciguatera symptoms after eating fish which do not cause symptoms in other persons (Narayan, 1980). Consumption of alcohol or chicken may have the same effect (Gillespie et al.,1986; Gillespie,1987). Such sensitisation can occur many months or even years after an attack of ciguatera. Both these factors are most troublesome in areas where people depend heavily on fish as their major dietary source of protein.

The basis for sensitisation and recurrent attacks tending to increase in severity is not known, but has been generally presumed to be immunological, although the symptoms are not typically allergic. A serum bank is being established at CSL Limited in Melbourne, Australia, as a basis for exploring the nature of sensitisation following ciguatera (Sutherland & Lewis,1992).

PATHOLOGY AND PATHOPHYSIOLOGY

Human pathological studies of ciguatera are few. Nakano (1983) reported high blood levels of creatine phosphokinase (CPK, a muscle enzyme) in 7 men affected with ciguatera on Midway Island, Central Pacific. The CPK level, initially >1000 IU/L (normal <200 IU/L) in each, returned to normal within 10 days. While their motor and sensory nerve conduction velocities remained normal, electromyography revealed changes consistent with an acute myopathic process. Insertional and spontaneous activity were normal. Mild recruitment (minimal effort) produced small motor units of short duration; maximal recruitment (maximal effort) revealed enhanced motor units of low amplitude. Repetitive nerve stimulation suggested possible neuromuscular junction fatigue in 2 patients. Muscle biopsies from 3 patients showed muscle fibre splitting, degeneration and necrosis, with subsarcolemmal tubular aggregates and small lipid vacuoles.

A near-fatal case in Hawaii was associated with prominent generalised muscle spasms and high blood levels of CPK (41,000 IU/L, reference range 45–35) and other muscle enzymes (Kodama et al.,1989). Palytoxin present in smoked mackerel from the Philippines was thought to be responsible. Similar cases have also been described following parrot fish ingestion in Japan (Noguchi et al.,1987). A possible association between polymyositis (a chronic inflammatory disease of muscle) and ciguatera occurring some years previously has been suggested (Stommel et al.,1991) but remains speculative.

The major morbidity of ciguatera, however, is probably attributable to its effects on peripheral nerves. Ayyar & Mullaly (1978) reported slowed sensory conduction velocities without decrease in sensory nerve action potential amplitude in affected patients. Other studies (Allsop et al.,1986; Cameron et al.,1991; Cameron & Capra,1991) documented increased distal motor and sensory latencies, reduced motor and sensory conduction velocities, prolongation of the absolute refractory, relative refractory and supernormal periods, reduced sensory amplitudes and F wave latencies. These findings are consistent with a neuropathic process which in traditional neurological terms is predominantly demyelinating rather than axonal in type (primarily damaging the myelin sheaths of nerves, which are part of Schwann cells, rather than the nerve fibres themselves).

The report of human nerve biopsy in ciguatera (Allsop et al.,1986) found striking edema of vacuoles in Schwann cell cytoplasm adaxonally (immediately abutting axons), with axonal compression and vesicular degeneration of myelin. Nakano (1983) described diffuse slowing of brain electrical activity, elevated cerebrospinal fluid pressures and abnormal brainstem auditory-evoked responses in ciguatera patients, although these are not common findings.

One interesting finding by Cameron & Capra (1991), in the rat tail nerve *in vivo*, is that a blood ethanol (alcohol) level of 0.05% was found to significantly increase the magnitude and duration of the abnormal supernormal response observed in ciguatoxin-treated rats. The mechanism of this potentiation, which is consistent with common clinical experience in humans, is yet to be elucidated. The nature of the human immune response to ciguatera is essentially unknown.

TREATMENT

Despite advances in understanding the nature and pharmacology of ciguatoxins, this has yet to translate into major specific therapeutic advances. No specific antidote is known for any of the many marine dinoflagellate toxins, including those causing ciguatera. Therapy remains primarily symptomatic and supportive. Many types of treatment have been tried and although some important uncontrolled observations have been reported, particularly in relation to man-

nitol, no double-blind controlled clinical trial results are available for any treatment modality.

Supportive and symptomatic therapy may include bed rest, analgesia, fluid and electrolyte replacement, airway protection and ventilatory support, circulatory support (including positive inotropic agents), management of dysrhythmias (most commonly bradycardias and atrioventricular block, occasionally necessitating temporary cardiac pacing), general care of the unconscious patient, antihistamines and cool showers for pruritis, hypnotics, etc. In French Polynesia standard (Bagnis et al.,1992) but unproven (Calvert,1991), therapy for hospitalised patients has consisted of intravenous infusions of vitamins C and B6 (pyridoxine) and calcium gluconate. A wide variety of traditional remedies, including a considerable number of plants, are used in various areas (Cooper,1964; Narayan, 1980; Amade & Laurent,1992; Dufva et al.,1976; Bourdy et al.,1992) Screening of traditional plant remedies with a novel mouse bioassay has found that an extract from leaves of *Argusia argenta* can reduce the effects of ciguatoxin (Amade & Laurent, 1992). Efficacy or safety in humans of traditional remedies are unknown.

Occasional success has been reported with low dose amitriptyline, a tricyclic antidepressant, particularly for chronic paraesthesia and other neurological symptoms (Bowman,1987; Davis & Villar,1986; Calvert et al.,1987). Fluoxetine (an antidepressant drug which is a relatively specific serotonin-uptake inhibitor) was reported to reduce chronic fatigue in two patients with ciguatera in whom symptoms had persisted for over nine months (Berlin et al.,1992). Nifedipine (a calcium channel blocker) (Calvert et al.,1987) and tocainide (a lignocaine-like local anaesthetic agent) (Lange et al.,1988; Lange & Kreider,1988) have some theoretical appeal but experience with their use is very limited.

The most dramatic reported experience of successful treatment of ciguatera has been that of Palafox et al. (1988) in the Marshall Islands, who treated 24 patients with acute ciguatera with intravenous infusions of mannitol, an osmotic diuretic agent most commonly used in the treatment of cerebral edema. Mannitol is inexpensive and readily available, but must be given by intravenous infusion and accompanied by careful patient monitoring. Two patients in coma and one in shock are reported to have responded within minutes, with full and rapid recovery, hitherto virtually unknown in severe ciguatera (recovery typically takes at least one, and more usually two weeks). Neurological and muscular manifestations improved dramatically; gastrointestinal symptoms resolved more slowly. A variety of case reports and uncontrolled observations involving small numbers of patients (Pearn et al., 1989; Williamson,1990; Stewart,1991) documented a clear clinical impression that in some patients (including young children) (Williams & Palafox,1990), mannitol is dramatically efficacious, notwithstanding the highly variable natural history of the disease. Patients at the more severe end of the disease spectrum and who are treated early (within 24 hours of symptom onset) would appear most likely to benefit from mannitol. The mechanism of action of mannitol in ciguatera is unclear - possibilities suggested (Pearn et al., 1989) include a direct anti-ciguatoxin effect via a scavenger mechanism, or an osmotic effect reducing Schwann cell edema, thereby ameliorating neurological dysfunction. Experimental studies on interactions between ciguatoxin and mannitol indicate that mannitol does not act to reduce the affinity of the sodium channel for ciguatoxin, nor does mannitol act as a scavenger for ciguatoxin (Lewis unpubl. data), suggesting that the osmotic effect is the most likely mode of action.

In the first controlled trial of mannitol (Bagnis et al.,1992) 34 patients were treated, compared with 29 patients treated with vitamins B6 and C and calcium. Patients were well matched, and a clinical score based predominantly on the number and severity of subjective symptoms showed significant benefit 1 and 24 hours after onset of treatment, particularly for paraesthesiae and gastrointestinal symptoms. The study suffers from a number of weaknesses: it is unclear whether the patients or the observers were blinded, the clinical score was based excessively on subjective criteria, no follow-up beyond 24 hours is reported, and the differences between treatment groups, while statistically significant, would appear not to be of major clinical significance. The clinical condition of some patients deteriorated in the first 24 hours despite mannitol infusion. Further studies of mannitol treatment are underway, at least in the Marshall Islands, Kiribati, Fiji and Florida. A rigorously conducted, double-blind controlled clinical trial, including as many objectively determined parameters as possible and with adequate follow-up is needed. At present, given the safety of mannitol and the rapidity with which benefit may be evident, the administration of mannitol would seem justified in patients whose illness is

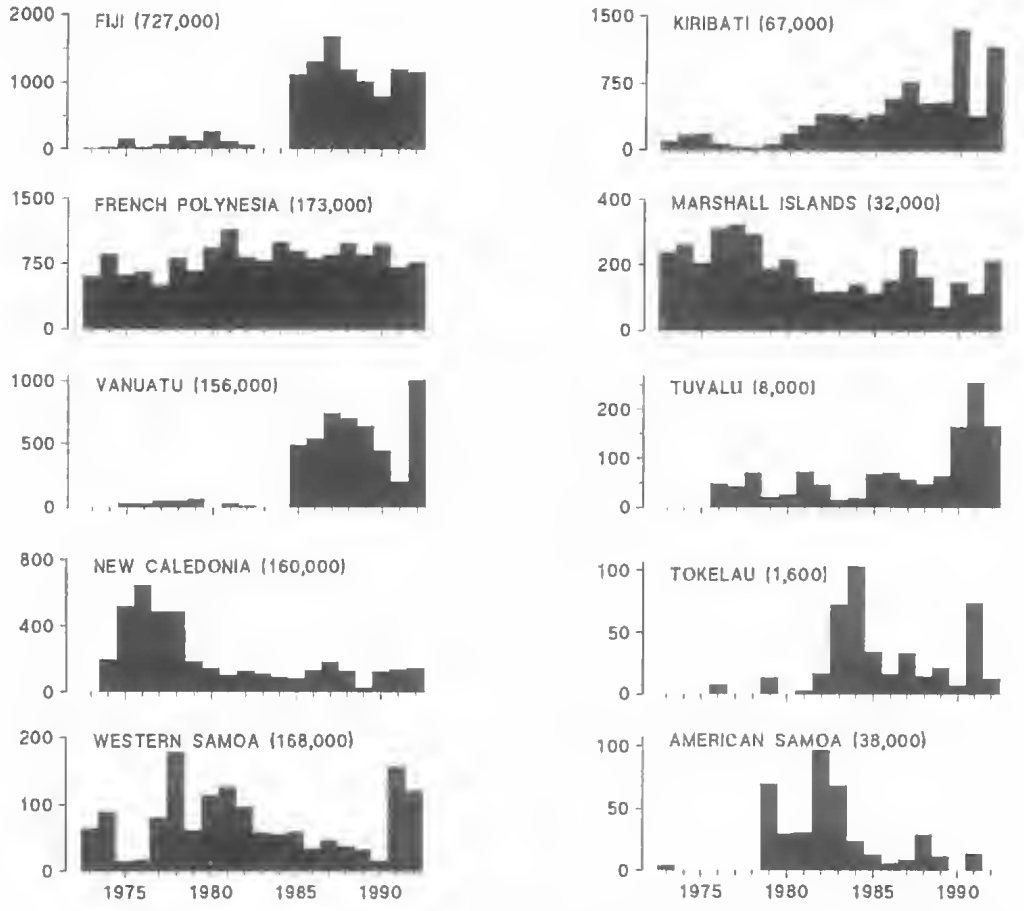

FIG. 1. Annual cases of ciguatera for selected Pacific countries, 1973-1992. Data from SPEHIS, 1973-1992. The 1988 population estimates for each country are indicated in parenthesis (FAO, 1990). Prior to 1982, data for the Marshall Islands also included data from the Federated States of Micronesia, the Northern Marianas and Palau.

moderate or severe, and particularly those who present during the acute phase of the illness, typically within 24 hours of the onset of symptoms. A dose of 1g mannitol per kg body weight, as a 20% solution, infused over about 30 minutes, has been most commonly used (Palafox et al., 1988; Pearn et al., 1989). The clinical impression is that half this dose, infused over 60 minutes, appears to be less effective (Pearn et al., 1989). No adverse experiences have been reported with use of mannitol in patients with ciguatera, but it is prudent to ensure that patients are replete in intravascular volume prior to commencement of mannitol infusion.

The remoteness of small and widely scattered island communities from health care services, particularly in the Pacific, imposes limitations on availability of medical treatments, particularly one requiring careful supervision and intravenous infusion. A safe orally-active therapy requiring minimal supervision is desirable.

All patients suffering from ciguatera should be advised to avoid fish and alcohol for at least 3 months, and to reintroduce them into their diet cautiously, recognising that ingestion of either may precipitate a relapse. Many sufferers of ciguatera, particularly in Western cultures and where fish are not a crucial foodstuff, lose all inclination to again eat reef fish.

INCIDENCE OF CIGUATERA

The most comprehensive regional database on ciguatera (SPEHIS, 1973-1992) also includes other forms of marine food poisoning (scombroid poisoning, clupeotoxism, mullet poisoning, puf-

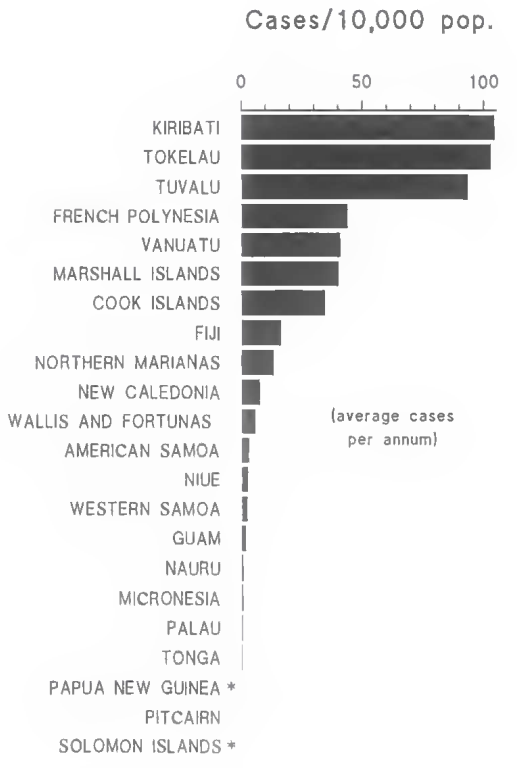

FIG. 2. Incidence of ciguatera in Pacific Island countries. Cases per 10,000 population are indicated Data are given per annum (p.a.) and were averaged from SPEHIS data (1973-1991) covering the period 1985-1990. Asterisks indicate incomplete reporting to SPEHIS from these countries.

fer fish poisoning and invertebrate intoxications). However, ciguatera typically dominates as a cause of fish poisoning in the Pacific region (Lewis,1992a). Ciguatera is reportedly prevalent throughout Pacific island countries with the exception of the Solomon Islands and Pitcairn Island (Fig.1). Ciguatera is invariably substantially underreported. In Australia it is estimated that as few as 20% of cases are reported and <10% of ciguatera cases in Western Samoa are reported to SPEHIS (Lewis, 1992a). Similar levels of underreporting are likely in other countries. Underreporting may vary within and between countries, and over time.

For countries of the South Pacific, the highest average incidence of reported ciguatera for the period 1985-1990 was c.100/10,000 population per annum(p.a.) in Kiribati, Tokelau and Tuvalu (Fig.2). The average reported incidence of ciguatera was less than half these levels in French Polynesia, Vanuatu, the Marshall Islands and the Cook Islands. The remaining 13 countries reported <15 cases/10,000 people p.a. Over the same period, the average reported incidence of ciguatera in Queensland (population 2.9 million) was 0.16 cases per 10,000 p.a., a level similar to that reported for Tonga. By way of comparison, in the Iles Saintes, Guadeloupe, in the Caribbean, annual ciguatera incidence has been estimated to be 30 (Czernichow et al.,1987), in the US Virgin Islands (Caribbean) to be 73 (Morris et al.,1982) and in Miami to be 5/10,000 population (Lawrence et al.,1980).

INDIRECT EFFECTS OF CIGUATERA

Throughout Pacific island countries there is a heavy dependence on the inshore fishery resource of reefs for dietary protein and animal fats. Johannes (1990) suggested that the inshore fisheries resource is of greater importance per capita to Pacific island countries than in any other region of the world. Nowhere is the impact of ciguatera greater than in atoll countries of the Pacific where intake of reef fish is often above 100g/per person per day (Lewis,1992a). Ciguatera is also important in relative terms, being one of the more commonly reported diseases (SPEHIS,1973–1991).

Ciguatera may have indirect effects on health by predisposing victims to poor nutrition and other diseases, and via its social and economic effects. The ability of subsistence communities to provide food, especially difficult on the poorer Pacific atolls, may be impaired due to the necessity of reducing fish consumption to reduce the risk of ciguatera (Lewis,1986). Ciguatera may have direct economic effects, reducing trade opportunities in potentially ciguateric fishes and damaging tourism (Lewis,1986). The effect of ciguatera on fish consumption is likely to be least in countries where alternative dietary protein sources to locally caught fish are costly and few, and where a system of traditional beliefs acts to reduce perceptions of the adverse effects of ciguatera (Lewis,1992a). People in larger and developed countries (e.g. Australia) with more diverse food sources and a less traditional orientation to the sea may be less accepting of ciguatera than are people in many Pacific Island countries.

The need to avoid fish after an outbreak of ciguatera may exacerbate undernutrition, especially among children (Eason & Harding,1987).

Fear of poisoning may accentuate dependence on imported food. In many Pacific locations, as much as 90% of fish eaten comes out of a can (Lewis,1986). Increased intake of imported food is often associated with a higher salt, fat and refined carbohydrate diet that contributes to an increase in chronic degenerative diseases such as diabetes (Zimmet et al.,1981), gout (Prior et al., 1987), hypertension (Zimmet et al., 1980) and atherosclerotic vascular disease (Taylor & Thoma,1985) in indigenous Pacific populations.

PREVENTION

Individual Level

Individuals can reduce their risk of contracting ciguatera by: 1, avoidance of warm water reef fish, particularly those with a known propensity to be toxic, and avoidance of certain pelagic fish which feed on them (e.g. barracuda and mackerel), especially in areas with a history of ciguatera; 2, avoidance of all fish at locations which are a known recent or current source of toxic fish. 3, complete avoidance of moray eels, which are commonly highly toxic (Murata et al.,1990; Lewis et al.,1991; Lewis et al.,1992), except when captured in areas with no history of ciguatera; 4, avoidance of carnivorous fish may reduce, but does not eliminate, the risk of contracting ciguatera. Ciguatoxins tend to be concentrated as they pass up the food chain, and larger fish (particularly 2.5kg) are more likely to be toxic (Hessel et al.,1960); 5, avoidance of the head, roe and viscera of potentially toxic fish. Concentrations of ciguatoxins in fish liver may be up to 50 times higher than in muscle (Banner, 1976); 6, eating a small portion (20–100g) from any one fish at the first sitting (Lewis,1992a); 7, feeding a large fish flesh meal to a cat which is observed for at least 6 hours prior to human consumption of portions of the same fish (Lewis,1992a; Cooper,1964); 8, washing the flesh of herbivorous fish (such as parrot and surgeon fish), in several changes of water prior to consumption has been recommended on the basis that this may remove some of the water-soluble maitotoxin (Juranovic & Park,1991). This has not, however, been demonstrated to be useful

Public Health Measures

These include: 1, education of fisherpeople and the public in affected areas about the risk of ciguatera and how this risk can be reduced (Ahmed,1991); 2, closure of known highly toxic areas to fishing (Ahmed,1991); 3, bans on the sale of high risk fish from known toxic locations. Such bans have been employed in American Samoa (Dawson,1977), Queensland (Lewis et al.,1988), French Polynesia (Lewis,1986), Fiji (Sorokin, 1975), Hawaii (Ahmed,1991; Gallop & Pon, 1992) and Miami (Craig,1980); apparently with some success, but with attendant economic loss; 4, detection of ciguatoxic fish prior to consumption. Such tests should be specific and sensitive for the toxins implicated in human disease. They should be sufficiently sensitive to detect 0.1 nM ciguatoxin-1 per kg of fish flesh (Lewis,1992b). To be used effectively at the community level, they should be robust, temperature-insensitive, reliable, inexpensive and simple to use.

Hokama pioneered development of such a test to detect ciguateric fish (Hokama,1991). A radioimmunoassay (RIA), subsequently modified to a simpler enzyme immunoassay (EIA) (Hokama, 1985) has been further simplified to a 'stick test' which has been used to screen fish caught in Hawaii (Hokama et al.,1990). All of 57 fish implicated in cases of ciguatera, and provided by the Hawaiian Department of Health in 1987-89 tested positive on a stick enzyme immunoassay (S-EIA) using a monoclonal antibody against ciguatoxin (MAb-CTX) (Hokama et al.,1990). All 86 *Caranx* sp (jack) and *Seriola dumerili* (amberjack) provided by sports fisherpersons and found to be negative on the S-EIA test, were consumed without incident (Hokama et al.,1990). However a high proportion, 1195/2190 (55%), of randomly tested fish of 19 different, potentially ciguatoxic species tested borderline or positive (Hokama et al.,1990), suggesting a high rate of false positive tests. The false negative rate however, which is of greater importance, would appear to be acceptably low.

Although the test has problems of specificity, cross-reacting with a variety of polyether toxins, such as okadaic acid, which play an uncertain role in ciguatera, and is not sufficiently robust to be used in the field (Hokama et al.,1990), it holds promise as a practical measure in ciguatera control, particularly for large fish processed commercially. Several groups are in the process of developing such antibody-based tests, including Hawaii Chemtec Inc, which plans to commercialize a modified version of the Hokama test. Research on detection of ciguatoxins using fluorescence high pressure liquid chromatography (HPLC) is also in progress. HPLC-based assays, perhaps linked to fluorescence or mass spectral detectors, have the potential to confirm ciguatoxins in small samples of fish flesh.

A rapid inexpensive test may eventually supplant the riskier process in use in some Pacific island areas, whereby an adult human eats or a cat is fed fish from an area, several times a year, to reassess the toxicity present in locally- caught reef fish. Such testing may be used particularly to protect children from ciguatera (Cooper,1964).

Long-term monitoring of populations of dinoflagellate(s) associated with ciguatera, their toxicity and toxicity of fish at various levels of the food chain at a range of sentinel sites may be of benefit in predicting ciguatera in an area. This may enable timely action, such as closing an area to fishing, or restricting types or sizes of fish caught, before an outbreak occurs (Ahmed, 1991). Such monitoring, particularly in areas of human impact on coral reefs (particularly through construction activities, other forms of coral damage, terrestrial and marine pollution, including sewage and agricultural runoff), could also make an important contribution to our understanding of the genesis of ciguatera. Such monitoring should be initiated with baseline studies prior to major developments likely to damage or alter a coral reef. There is widespread concern, particularly in the Pacific, that coral reef damage and pollution associated with population increase and economic development may increase the incidence of ciguatera (Lewis,1992a, Lewis,1986). The possible effects of global warming, stratospheric ozone depletion and other global environmental changes on ciguatera are unknown and provide additional justification for long-term environmental monitoring.

Restriction of human activities likely to be associated with coral reef damage. In some Pacific islands, such as the Line islands (Ross,1947), Gilbert Islands (Cooper,1964), and Hao, Moruroa and Mangareva in French Polyncsia (Ruff,1989a,b) military dumping of material on reefs, construction activities and nuclear test explosions have been associated with outbreaks of ciguatera. Similarly, outbreaks have followed shipwrecks, shore modification and other construction activities in the Marquesas (Lewis, 1984a) and Hawaii (Gallop & Pon,1992; Lewis, 1984b). Although not supported by firm data, local Aboriginal people in East Arnhem Land ascribe the occurrence of ciguatera near the Gove peninsula to the construction of a township and alumina plant at Nhulunbuy in the early 1970s.

FUTURE DEVELOPMENTS

Key issues and areas for research include: 1, the need for a consistent case definition of ciguatera, a crucial basis for comparable epidemiologic and clinical data; 2, better tests for ciguatoxins, including ones which can be applied to human clinical samples. Antibodies which are more selective and have higher affinity for the ciguatoxins than those currently available are needed; 3, understanding of the pathophysiological mechanisms underlying human disease, potentiation of the disease by alcohol, and the phenomenon of sensitisation; 4, understanding of the human immune response to ciguatera may provide a basis for more effective control, particularly through immunisation; and 5, treatment for ciguatera which is simple to administer (preferably orally), inexpensive, and which is demon-strated to be effective and safe. In the short term, a well-conducted randomised controlled double-blind trial of mannitol therapy is needed.

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